48. (New) A method of claim 46, wherein the immunoglobulin polypeptide or fragment thereof is human.

49. (New) A method of claim 46, wherein the immunoglobulin polypeptide is a monoclonal antibody raised against an amyloid fibril.

REMARKS

Status of the Claims

Claims 1-23, and 25-27 have been canceled without prejudice or disclaimer of the subject matter claimed therein. Accordingly, claims 24 and 28-45 are pending in the instant application.

The elected species for consideration at this time is monoclonal antibodies reactive with a non-light chain amyloid. Claims 28 and 36, directed to antibodies raised against the immunoglobulin light chain, are withdrawn from consideration at this time by the Examiner. Thus, claims 24, 29-35, and 37-45 are pending for consideration before the Office.

Declaration Under 37 C.F.R. § 1.132 and References Cited in Amendment and Declaration

The Declaration under 37 C.F.R. § 1.132 was originally submitted with the response to the Office Action of October 23, 2002. A copy of the Declaration is attached.

The references cited in the Declaration under 37 C.F.R. § 1.132 and in this amendment are listed on the PTO Form 1449 and are accompanied with an Information Disclosure Statement. Since a copy of each of these references was submitted with the response to the Office action of October 23, 2002, these references are not resubmitted with the present amendment.

Rejection Under 35 U.S.C. § 102

Claims 23-27, 29-31, 35, 40-42, and 45 were rejected under 35 U.S.C. § 102(b) as being anticipated by Konig *et al.* (WO 96/25435) in the previous Office Action.

Pending claims 24 and 29-31, 35, 40-42, and 45 are directed to a method of removing amyloid deposits comprising administering to the patient an immunoglobulin polypeptide or fragment thereof that binds to an amyloid fibril or component or precursor thereof. Konig *et al.*

merely disclose methods of generating antibodies against the Aβ peptide and methods of using the antibodies to detect amyloid plaques in post-mortem tissue. The cited reference shows only the results of immunohistochemical studies performed with the antibodies. Specifically, Konig *et al.* use the antibodies to stain amyloid plaques in a formic acid treated, paraffin embedded 10 μm thick section from a postmortem brain. Respectfully, Konig *et al.* do not disclose administering the antibodies to a patient for any reason, let alone to remove amyloid deposits. Moreover, Konig *et al.* do not show that their antibodies are able to remove amyloid deposits from a patient.

Applicants respectfully submit that a claim is anticipated if each and every element as set forth in the claim is found in the prior art, either expressly or inherently. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). See also MPEP § 2131. Given this absolute requirement for the teachings of a reference under 35 U.S. C. § 102, the pending rejection over Konig *et al.* cannot be maintained because Konig *et al.* do not teach the claimed method of administration to remove amyloid deposits. If the Office intends to rely on some unstated inherent property of the antibodies disclosed by Konig *et al.*, Konig *et al.* still do not describe the claimed method step of administering an immunoglobulin or fragment thereof to a patient. Further, as discussed in the attached declaration of Dr. Anja Leona Bier, the usefulness of antibodies as a diagnostic tool in binding and detecting amyloid plaques does not suggest that the antibodies are effective in removing amyloid plaques from a patient. Accordingly, Konig *et al.* do not anticipate the claimed invention. Applicants respectfully request the withdrawal of the rejection.

Rejection Under 35 U.S.C. § 103(a)

Claims 23-27, 29-35, and 37-45 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Walker *et al.*, Konig *et al.*, Becker *et al.* (Nettleship *et al.*) and *Immunology: A Short Course* (Benjamini & Leskowitz Ed.).

Pending claims 24, 29-35, and 37-45 as they stand are directed to a method of removing amyloid deposits comprising administering to the patient an immunoglobulin polypeptide or fragment thereof that binds to an amyloid fibril or component or precursor thereof.

Walker *et al.* disclose a diagnostic method for detecting amyloid deposits comprising injecting monoclonal antibody 10D5 into the cerebrospinal fluid of the brain of a monkey and detecting amyloid deposits by performing postmortem immunohistochemistry on a para-formaldehyde fixed tissue section of the brain of a monkey. Walker *et al.* use the 10D5 antibody as a diagnostic tool to bind and label amyloid deposits for detection in the monkey's brain. Walker *et al.* neither teach the use of the antibody to remove amyloid deposits in a patient comprising administering the 10D5 antibody to the patient nor show that the 10D5 antibody is capable of removing amyloid deposits from a patient. Respectfully, it is not predictable that the 10D5 antibody would be effective in removing amyloid deposits from a patient.

Likewise, Konig *et al.* do not disclose a method of administering antibodies to a patient to remove amyloid deposits from the patient. Konig *et al.* show that the Mab 369.2B antibody is a useful postmortem diagnostic agent for *in vitro* immunohistochemical studies. As discussed in the attached declaration of Dr. Anja Leona Bierc, the effectiveness of an antibody as an *ex vivo* or *in vitro* diagnostic tool does not suggest its effectiveness as an agent for removing amyloid deposits from a patient. Moreover, Mab 369.2B has not been tested for *in vivo* administration. It is not even predictable that Mab 369.2B would remove an amyloid deposit in an *in vivo* system. Thus, Konig *et al.* do not provide the missing elements of Walker *et al.* to render the claimed invention obvious.

Similarly, Becker *et al.* (Nettleship) do not teach a method of treatment comprising administering antibodies to a patient to remove amyloid deposits. Although Becker *et al.* generally discuss using antibodies having a specificity for β-amyloid peptide for diagnostic and, hypothetically, for therapeutic purposes, they fail to disclose any examples of the use of such an antibody for the specific purpose of removing amyloid deposits from a patient. The focus of the disclosure is the use of such an antibody in *in vitro* diagnostic screening assays for potential inhibitors of β-amyloid neurotoxicity. At the time of Applicants' invention, it was not predictable that such an antibody would be effective in removing amyloid deposits from a patient. Accordingly, Becker *et al.* do not contain the elements missing from Walker *et al.* and Konig *et al.* to render the claimed invention obvious.

Benjamini is cited because it provides a definition for "opsonization." However, none of the other three cited references suggest that the antibodies disclosed therein are acting as opsonins.

The claimed invention is directed to a method of removing amyloid deposits in a patient comprising administering to the patient an immunoglobulin polypeptide or fragment thereof that binds to an amyloid fibril or component or precursor thereof. Applicants unexpectedly showed that antibodies against amyloid fibrils are effective in removing amyloid deposits *in vivo*. Thus, Applicants unexpectedly discovered a method of treating a patient suffering from amyloid deposits comprising administering antibodies to the patient to remove amyloid deposits.

The attached declaration under 37 CFR § 1.132 by Dr. Anja Leona Bierc, a scientist in the field of amyloidosis, sets forth the state of the art at the time of Applicants' invention and the reasons that Applicants' claimed method of treatment comprising administering antibodies to remove amyloid deposits from patients is not obvious in view of the cited references.

At the time of Applicants' invention, the only treatment available for patients with systemic amyloid-associated diseases involved attempting to reduce the synthesis of the amyloidogenic precursor protein, *e.g.*, in cases of primary (AL) amyloidosis, such therapy involved the use of anti-plasma cell chemotherapy given in conventional doses or high doses in combination with autologous stem cell transplantation (in rare instances, localized amyloid deposits such as in the larynx or bladder were removed surgically); for secondary (AA) amyloidosis, administration of anti-inflammatory agents (Falk *et al.*, *The New England Journal of Medicine*, 1997, 337 (13): 898-908; Schehr, R., *BioTechnology*, 1994, 12:140-144); for hereditary amyloidosis (ATTR), liver transplantation (Holmgren *et al.*, *Lancet*, 1993, 341:1113-1116). None of these approaches for treating patients with primary, secondary, or hereditary forms of amyloidosis renders the claimed method of treatment discovered by Applicants obvious. Further, prior to Applicants' invention, no treatment was available for removing amyloid deposits in other amyloid-associated systemic diseases, *e.g.*, type 2 diabetes, or in amyloid-associated brain disorders, *e.g.*, Alzheimer's disease.

In fact, at the time of Applicants' invention, the focus of the amyloidosis research was inhibiting formation of the precursor protein with agents other than antibodies (Kisilevsky, R, *Drugs & Aging*, 1996; 8 (2):75-83). Scientists in the field of amyloidosis research at the time of

Applicants' invention would not have considered the use of antibodies as a viable treatment option because it was believed that amyloid deposits in patients were not recognized by the human body as foreign materials that would induce a humoral (antibody-based) immune response.

Further, as discussed in the declaration, though the use of antibodies as research tools and for diagnostic purposes was known to the skilled artisan at the time of Applicants' invention, it was not predictable that antibodies capable of binding and detecting amyloid deposits *in vitro* would have been effective in actually removing amyloid deposits from patients *in vivo*. The mere binding of an antibody to amyloid fibril for diagnostic purposes is not sufficiently predictive of its ability to remove amyloid fibril from a patient.

Accordingly, due to the unexpected nature of the invention and for the reasons discussed above, the combination of the cited references simply do not render the claimed invention obvious.

CONCLUSION

In view of the accompanying remarks, Applicants respectfully request reconsideration and timely allowance of the pending claims. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact Applicants' undersigned representative to expedite prosecution.

If there is any fee due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

Sally P. Tong
Reg. No. 45,397

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Customer No. 09629
MORGAN, LEWIS & BOCKIUS LLP
1111 Pennsylvania Ave., N.W.
Washington, D.C. 20004
(202) 739-3000